REMARKS

Claims 15-20 and 37-40 are currently pending and under consideration.

Applicants acknowledge and appreciate the withdrawal of the rejection under 35 U.S.C. § 112, Second Paragraph.

I. The Rejection of Claims 15-17, 19, 20, 37, and 39 under 35 U.S.C. 102(e)

Claims 15-17, 19, 20, 37, and 39 remain rejected, allegedly, as anticipated by U.S. Patent No. 5,811,523 to Trinchieri *et al.* ("the '523 patent") as evidenced by U.S. Patent No. 5,780,597 to Gatley *et al.*, Carter *et al.*, 1997, *Hybridoma* 16(4), and Colman *et al.*, 1994, *Res. Immunol.* 145(1):33-36. In particular, the Examiner states that the '523 patent teaches a polyclonal and monoclonal antibody to the human cytokine NKSF heterodimer (IL-12), that specifically reacts with the 35 kD subunit of NKSF and alleges that the antibody taught by the '523 patent inherently has the same functional properties as the antibodies of the present invention.

In response, Applicants respectfully disagree and submit that the '523 patent does not teach each and every element of the claimed invention and that the antibody taught by the '523 patent does not necessarily possess the same properties as the antibodies of the present invention. Accordingly, the rejection of claims 15-17, 19, 20, 37, and 39 as anticipated, either explicitly or inherently, by the '523 patent is in error.

The claimed subject matter is not explicitly taught by the cited references. Each of claims 15 and 16 recites a monoclonal antibody that immunologically reacts with the p75 heterodimer of human IL-12, but not any epitope of the p40 subunit. These monoclonal antibodies neutralize at least about 90% of the bioactivity of human IL-12 in either of two specific assays when the concentration of the antibody is 0.5 μg/ml and the concentration of human IL-12 is 0.25 ng/ml. The neutralization of bioactivity of human IL-12 can be assessed in either an IL-12 stimulated PHA-activated human lymphoblast proliferation assay or an IL-12 stimulated IFN-γ production assay. Thus, the antibodies of the present invention neutralize at least about 90% of the bioactivity of human IL-12 when the antibody and human IL-12 are present at defined concentrations, as recited by, for example, claims 15 and 16. Claims 17, 19, 20, 37, and 39 ultimately depend from either claim 15 or 16, and, thus, all of the allegedly anticipated claims recite the above-described limitation.

The '523 patent does not explicitly teach that the antibodies described therein can neutralize at least about 90% of the bioactivity of human IL-12 when the concentration of the

antibody is 0.5 μg/ml and the concentration of human IL-12 is 0.25 ng/ml. Indeed, the '523 patent does not characterize the described antibody in any way beyond the specificity of the antibody for NKSF or one of the subunits thereof. To prove that a claim is anticipated, *all* the elements of the claim must be present in a *single* prior art reference, and a reference that omits even one limitation of a claim does not anticipate. *Jamesbury Corp. v. Litton Indus. Prods.*, 756 F.2d 1556, 1563; 225 U.S.P.Q. 253, 259 (Fed. Cir. 1985). It is clear in view of the foregoing, that the claimed subject matter is not explicitly disclosed by the'523 patent.

With regard to inherent anticipation, in order for the '523 patent to inherently anticipate the claims of the present invention, the antibody taught by the '523 patent must, inevitably and necessarily, neutralize at least about 90% of the bioactivity of human IL-12 when the concentration of the antibody is 0.5 μg/ml and the concentration of human IL-12 is 0.25 ng/ml.

Inherent anticipation occurs when a prior art reference discloses a process that inevitably generates a later-claimed product. *See, e.g., Mehl/Biophile International Corp. v. Milgraum*, 192 F.3d 1362; 52 U.S.P.Q.2d 1303 (Fed. Cir. 1999); *Glaxo v. Novopharm Ltd.*, 52 F.3d 1043, 1047; 34 U.S.P.Q.2d 1565, 1567 (Fed. Cir. 1995). An anticipating reference must allow the person of ordinary skill to make the claimed invention without further research or experimentation. *In re Hall*, 781 F.2d 897, 899; 228 U.S.P.Q. 453, 455 (Fed. Cir. 1986). "[P]rior art references must be evaluated on what they taught or suggested in their entireties when the invention was made, not on hypothetical modifications made with knowledge of the invention in suit many years later." *Panduit Corp. v. Dennison Mfg. Co.*, 774 F.2d 1082, 1095; 227 U.S.P.Q. 337, 346 (Fed. Cir 1985), *vacated and remanded*, 475 U.S. 809 (1986), *reaffirmed on remand*, 810 F.2d 1561, 1575 n.33; 1 U.S.P.Q.2d 1593, 1603 (Fed. Cir.); *see also Carl Schenck, A.G. v. Nortron Corp.*, 713 F.2d 782, 787; 218 U.S.P.Q. 698, 702 (Fed. Cir. 1983). Extrinsic evidence may properly be used to show that a claim limitation is *inherently* disclosed because it flows naturally from what the reference conveyed to those of ordinary skill in the art. However, the extrinsic evidence relied on "must make clear that the missing descriptive matter is necessarily present in the thing described in the reference" (emphasis added) *In re Robertson*, 169 F.3d 743, 745; 49 U.S.P.Q.2d 1949, 1950-1951 (Fed. Cir. 1999); *Tronzo v. Biomet, Inc.*, 156 F.3d 1154, 1159; 47 U.S.P.Q.2d 1829, 1834 (Fed. Cir. 1998); *Continental Can Co. USA v. Monsanto Co.*, 948 F.2d 1264, 1268; 20 U.S.P.Q.2d 1746, 1749 (Fed. Cir. 1991). Moreover, inherency cannot be proven by possibilities, or even probabilities. *In re Oelrich*, 666 F.2d 578, 581; 212 U.S.P.Q. 323, 326 (C.C.P.A. 1981) (quoting *Hansgrig v. Kemmer*, 102 F. 2d 212, 214; 40

U.S.P.Q. 665, 667 (C.C.P.A. 1939); *see also In re Robertson*, 169 F.3d at 746; 49 U.S.P.Q.2d at 1951; *Continental Can.*, 948 F.2d at 1269; 20 U.S.P.Q.2d at 1749.

Even when a process is explicitly disclosed in a prior art reference, its mere *potential* to form the claimed product cannot prove anticipation. Substantial uncertainty regarding whether a compound actually was produced precludes anticipation. *See, W.L. Gore v. Garlock, Inc.*, 721 F.2d 1540, 1544, 220 U.S.P.Q. 303, 314 (Fed. Cir. 1983) ("given the unique nature of [the claimed product], we are not persuaded that the 'effect' of the processes disclosed . . . would be always to inherently produce or be seen always to produce products meeting all the claim limitations. Anticipation . . . cannot be predicated on mere conjecture respecting the characteristics of products that might result from the practice of processes disclosed in references"). The expressly disclosed process must *necessarily and inevitably* produce the claimed product with the inherent characteristics. *Mehl*, 192 F.3d at 1365, 52 U.S.P.Q.2d at 1305; *Glaxo*, 52 F.3d at 1047, 34 U.S.P.Q.2d at 1567. Moreover, inherency cannot be established if even only one attempted reproduction of the claimed subject matter fails. *See Glaxo*, 52 F.3d at 1047-1048, 34 U.S.P.Q.2d at 1567 (non-anticipation affirmed where patent assignee's employee and expert witness failed to reproduce a chemical form, despite the fact that defendant's experts had reproduced it 13 times). Thus, in order for the '523 patent to inherently disclose the claimed antibodies, any antibody specific for IL-12, including those disclosed in the instant specification or in the '523 patent, must inevitably and necessarily have the same bioactivity. However, this is not the case, as described below.

Applicants respectfully submit that the antibodies that specifically bind human IL-12 as taught by the '523 patent do not necessarily neutralize at least about 90% of the bioactivity of human IL-12 when the concentration of the antibody is 0.5 μg/ml and the concentration of human IL-12 is 0.25 ng/ml. In fact, the present application compares the ability to neutralize human IL-12 bioactivity of the antibodies of the invention to that of an antibody identified as 20C2. 20C2 specifically binds the p75 heterodimer of IL-12, but does not react with either the p35 or the p40 subunit alone. *See*, for example, D'Andrea *et al.*, 1992, *J. Exp. Med.* 176:1387-1398 at page 1391, col. 2, bridging paragraph from page 1390 and at page 1395, col.2, second full paragraph (Reference C4 of record).

Moreover, the present application demonstrates that the while 20C2 specifically binds IL-12, it nonetheless does not neutralize at least about 90% of the bioactivity of human IL-12 when those molecules are present at the recited concentrations. *See*, for example, the specification at page 4, line 25 to page 6, line 2 and Figures 3 and 5. Figure 3 shows that the monoclonal antibodies of the invention can neutralize at least about 90% of the bioactivity of

0.25 ng/ml human IL-12 as assessed by an IL-12 stimulated PHA-activated lymphoblast proliferation assay, while 20C2 simply cannot. Likewise, Figure 5 shows that the monoclonal antibodies of the invention can neutralize at least about 90% of the bioactivity of 0.25 ng/ml human IL-12 in an IFN-γ production assay, while 20C2 cannot. Thus, though 20C2 specifically binds human IL-12, it does not neutralize at least about 90% of human IL-12 bioactivity.

As shown by the foregoing, the present application provides an example of an antibody that specifically reacts with human IL-12 but does not neutralize at least about 90% of the bioactivity of human IL-12 when the concentration of the antibody is 0.5 μg/ml and the concentration of human IL-12 is 0.25 ng/ml. Thus, it is clear that an antibody that specifically reacts with human IL-12 does not inevitably and necessarily neutralize at least about 90% of the bioactivity of human IL-12 as required by the claims. Inherency cannot be established if just one attempted reproduction fails. *See Glaxo*, 52 F.3d at 1047-1048, 34 U.S.P.Q.2d at 1567. Accordingly, the '523 patent does not inherently teach this element of the invention as presently claimed because an antibody specific to IL-12 has been shown to have a different bioactivity, thus demonstrating that not all antibodies to IL-12 necessarily and inevitably have the same bioactivity.

With regard to the Examiner's assertion that the burden of showing non-anticipation is on the applicant, Applicants note that the Examiner cannot shift the burden to Applicants to show that the claimed invention is not anticipated. As discussed above, only when the Examiner sets out a basis in fact and/or technical reasoning to show that the cited reference inevitably and necessarily possesses the allegedly inherent characteristic can the burden be shifted to Applicants to show a non-obvious difference between the reference and the claimed invention. The Examiner has not shown and cannot demonstrate that the antibodies of the '523 patent necessarily neutralize at least about 90% of the bioactivity of human IL-12 when the concentration of the antibody is 0.5 μg/ml and the concentration of human IL-12 is 0.25 ng/ml. Accordingly, the burden remains on the Examiner to prove that the presently claimed antibodies are not patentable in order to reject the claims of the present application.

In conclusion, the '523 patent does not teach, either explicitly or inherently, each and every element of the invention as presently claimed in view of the production of antibodies to IL-12 that do not have the specified bioactivity as claimed. Therefore, Applicants respectfully submit that the rejection of claims 15-17, 19, 20, 37, and 39 under 35 U.S.C. § 102(b) is in error and must be withdrawn.

II. The Rejection of Claims 15, 16, 18, and 38-40 under 35 U.S.C. § 103(a)

Claims 15, 16, 18, and 38-40 remain rejected under 35 U.S.C. § 103(a), allegedly, as obvious over the '523 patent in view of U.S. Patent No. 5,780,597 to Gately *et al.*; Carter *et al.*, 1997, *Hybridoma* 16(4); Colman *et al.*, 1994, *Res. Immunol.* 145(1):33-36; and Bendig, 1995, *Methods: A Companion to Methods in Enzymology* 8:83-95. Applicants respectfully disagree and submit that the cited references, either alone or in combination, do not teach, much less suggest, each and every element of the invention as presently claimed.

As discussed above, the claims are directed to a monoclonal antibody that immunologically reacts with the p75 heterodimer of human IL-12, but not any epitope of the p40 subunit, and which antibody neutralizes at least about 90% of the bioactivity of human IL-12 when the concentration of the antibody is 0.5 μg/ml and when the concentration of human IL-12 is 0.25 ng/ml. Claims 18 and 38-40 ultimately depend from either claim 15 or 16, and, thus, all the claims rejected allegedly as nonobvious recite the above-described limitations.

The rejection of Claims 15, 16, 18, and 38-40 is allegedly supported, in part, on the same portions of the '523 patent as were cited in the rejection of claims 15-17, 19-20, 37, and 39 under Section 102 above. In particular, the Examiner relies upon the '523 patent to teach or suggest an antibody that neutralizes at least about 90% of the bioactivity of human IL-12 when the concentration of the antibody is 0.5 μg/ml and the concentration of human IL-12 is 0.25 ng/ml.

However, as shown above, the '523 patent in no way teaches or suggests an antibody that neutralizes at least about 90% of the bioactivity of human IL-12 when the concentration of the antibody is 0.5 μg/ml and the concentration of human IL-12 is 0.25 ng/ml. This deficiency of the '523 patent is not remedied by the disclosures of the other cited references.

A rejection for obviousness is improper when there is nothing in the cited prior art references, either singly or in combination, to suggest the desirability of the claimed subject matter. For a rejection of claimed subject matter as obvious in view of a combination of prior art references to be upheld, (1) the prior art must have suggested to those of ordinary skill in the art that they should make the claimed composition or device or use the claimed method, as the case may be; and (2) the prior art must have revealed that in so doing, those of ordinary skill would have had a reasonable expectation of success. *In re Vaeck*, 947 F.2d 488, 20 USPQ2d 1438 (Fed. Cir. 1991); *In re Dow Chemical Co.*, 837 F.2d 469, 5 USPQ2d 1529 (Fed. Cir. 1988). None of the cited references teach or suggest an antibody that neutralizes at

least about 90% of the bioactivity of human IL-12 when the concentration of the antibody is 0.5 μg/ml and the concentration of human IL-12 is 0.25 ng/ml.

Therefore, in view of the above, none of the cited references teach or suggest this element of the invention as presently claimed. Accordingly, Applicants respectfully submit that the rejection of claims 15, 16, 18, and 38-40 as obvious under 35 U.S.C. § 103(a) is in error and request its withdrawal.

CONCLUSION

In view of the above remarks, Applicants respectfully submit that the claims fully comply with all statutory requirements for patentability. Accordingly, Applicants respectfully request reconsideration of the claims of this application with a view towards allowance. The Examiner is invited to telephone the undersigned attorney, if the Examiner feels that a teleconference could help resolve any outstanding issues.

Respectfully submitted,

by William V. Quinn
REG NO 40,207

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Thomas E. Friebel 29,258
Thomas E. Friebel (Reg. No.)

JONES DAY
222 East 41st Street
New York, New York 10017
(212) 326-3939